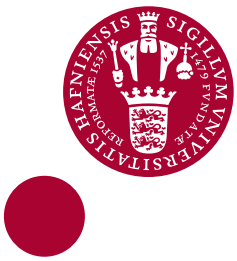

Condensyl® and decreases sperm DNA damage which is a risk factor for male infertility: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006

(Scientific Opinion)

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

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Condensyl® and decreases sperm DNA damage which is a risk factor for male infertility: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA),
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Abstract

Following an application from Laboratoire Nurilia submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to 'Condensyl® and decreases sperm DNA damage. High sperm DNA damage is a risk factor for male subfertility/infertility'. Condensyl® is a fixed combination of opuntia fruit dry extract, *N*-acetyl cysteine, zinc, nicotinamide, vitamins B2, B6, B12 and E, and folic acid. The Panel considers that Condensyl® is sufficiently characterised. The Panel assumes that the disease that is the subject of the application is male infertility and that the target population for the claim includes males wishing to increase their fertility but excludes males with clinical infertility. The Panel considers that the reduction of DNA sperm damage is a beneficial physiological effect in the context of reducing the risk of male infertility. The applicant provided four human intervention studies conducted in males with clinical infertility, from which no conclusions could be drawn for the scientific substantiation of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of Condensyl® and reduction of DNA sperm damage in the context of reducing the risk of male infertility.

Keywords: Condensyl®, fertility, sperm DNA, health claim

Requestor: Competent Authority of France following an application by Laboratoire Nurilia

Question number: EFSA-Q-2016-00665

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Summary

Following an application from Laboratoire Nurilia submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to 'Condensyl® and decreases sperm DNA damage. High sperm DNA damage is a risk factor for male subfertility/infertility'.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The general approach of the NDA Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on health claim applications.

The food which is proposed by the applicant to be the subject of the health claim is Condensyl®, a tablet containing a fixed combination of opuntia fruit dry extract (Nopal pulpe violin powder) (100 mg), *N*-acetyl cysteine (250 mg), zinc (15 mg), nicotinamide (16 mg), vitamin E (succinate) (12 mg), vitamin B6 (pyridoxine) (1.4 mg), vitamin B2 (riboflavin) (1.4 mg), folic acid (0.40 mg) and vitamin B12 (cyanocobalamin) (2.5 μg). Nopal (*Opuntia ficus indica* (L.) Mill.) powder is standardised for the content of quercetin (5 mg/100 g), indicaxanthin (13.2 mg/100 g) and betanin (28.8 mg/100 g). The Panel considers that the food/constituent Condensyl®, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is 'reduction of sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index), high sperm DNA damage being a risk factor for male subfertility/infertility'. The proposed target population is 'males in reproductive age with unknown reason leading to subfertility'.

The Panel notes that the term 'subfertility' has not been defined by the applicant. The Panel also notes that infertility is clinically defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

In this context, the Panel assumes that the disease that is the subject of the application is male infertility and that the target population for the claim includes males wishing to increase their fertility but excludes males with clinical infertility.

The Panel notes that the applicant did not provide evidence to establish that a reduction of sperm DNA damage decreases the risk of male infertility. Therefore, the Panel considers that the reduction of DNA sperm damage is a beneficial physiological effect in the context of reducing the risk of male infertility, as long as evidence is provided that Condensyl® induces a reduction in both DNA sperm damage and male infertility.

The applicant provided four human intervention studies as being pertinent to the claim. The Panel notes that all these studies were conducted in males with established clinical infertility and that they relate to the treatment of the disease, and therefore, the effect of the intervention on the incidence of male infertility cannot be assessed. In addition, the Panel notes that two of these studies had no control group, and that a third study was conducted with a product not complying with the specifications of the food for which the claim is proposed. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

In the absence of evidence for an effect of Condensyl® in reducing sperm DNA damage and the risk of male infertility *in vivo* in humans, the studies provided by the applicant on the proposed mechanisms by which Condensyl® could exert the claimed effect were not considered by the Panel for the scientific substantiation of the claim.

On the basis of data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of Condensyl® and reduction of DNA sperm damage in the context of reducing the risk of male infertility.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006[1] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14–17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to of this Regulation, an application for shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: Condensyl® and decreases sperm DNA damage.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Condensyl®, a positive assessment of its safety, nor a decision on whether Condensyl® is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

2.1.1. Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food constituent that is the subject of the claim is Condensyl®, a fixed combination of opuntia fruit dry extract standardised in quercetin and betalain, *N*-acetyl cysteine, zinc, vitamin B3, E, B6, B2, B9 and B12.

Health relationship as claimed by the applicant

According to the applicant, the food Condensyl® reduces sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index), high sperm DNA damage being a risk factor for male subfertility/infertility.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

According to the applicant, the effect of Condensyl® could be explained by boosting *S*-Adenosyl Methionine (SAM) production by folic acid as the methyl donor, and all the cofactors for the concerned enzymes, namely vitamins B2, B3, B6 and B12, and zinc. The synthesis of glutathione (GSH) is supported by the SAM (activating cystathionine β-synthase - CBS) induced as such and further boosted by the supplementation of acetyl cysteine acting as the cysteine donor and zinc and vitamin B6 as the necessary CBS cofactors. Small amount of vitamin E, quercetin and betalains from nopal provide some protection to the cell membranes from excessive peroxidation.

[1] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'The combination of opuntia fruit dry extract standardised in quercetin and betalain, N-acetyl cysteine, zinc, vitamin B3, E, B6, B2, B9 and B12 in Condensyl® decreases sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index). High sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index) is a risk factor for male subfertility/infertility'.

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of two tablets of Condensyl® daily. The target population proposed by the applicant is the healthy male population with high DNA fragmentation index (DFI) and high nuclear decondensation index (SDI).

Data provided by the applicant

Health claim application on Condensyl® decreases the sperm DNA damage. High sperm DNA damage is a risk factor for male dysfertility/infertility pursuant to Article 14 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims.[2]

As outlined in the General guidance for stakeholders on health claim applications,[3] it is the responsibility of the applicant to provide the totality of the available evidence.

This health claim application does not include a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.

Data related to the manufacturing process of Condensyl® presented in the application are confidential to Laboratoire Nurilia.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016).

3. Assessment

3.1. Characterisation of the food/constituent

The food/constituent which is proposed by the applicant to be the subject of the health claim is Condensyl®, a tablet containing a fixed combination of opuntia fruit dry extract (Nopal pulpe violin powder) (100 mg), *N*-acetyl cysteine (250 mg), zinc (15 mg), nicotinamide (16 mg), vitamin E (succinate) (12 mg), vitamin B6 (pyridoxine) (1.4 mg), vitamin B2 (riboflavin) (1.4 mg), folic acid (0.40 mg) and vitamin B12 (cyanocobalamin) (2.5 μg). Nopal (*Opuntia ficus indica* (L.) Mill.) powder is standardised for the content of quercetin (5 mg/100 g), indicaxanthin (13.2 mg/100 g) and betanin (28.8 mg/100 g). The total weight of the tablet is 880 mg.

An overview of the manufacturing process, batch-to-batch variability and stability data were provided.

The Panel considers that the food/constituent Condensyl®, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'reduction of sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index), high sperm DNA damage being a risk factor for male subfertility/infertility'. The proposed target population is 'healthy males with high DNA Fragmentation Index (DFI) and Nuclear Decondensation Index (SDI)'. Upon a request for clarification from EFSA, the applicant stated that the target population for the claim is 'males in reproductive age with unknown reason leading to subfertility'.

[2] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Sjödin A, Stern M, Tomé D, Van Loveren H, Vinceti M, Willatts P, Martin A, Strain JJ, Heng L, Valtuena Martınez S and Siani A, 2017. Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 2). EFSA Journal 2017;15(1):4680, 31 pp. https://doi.org/10.2903/j.efsa.2017.4680

[3] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. https://doi.org/10.2903/j.efsa.2016.4367

The Panel notes that the term 'subfertility' has not been defined by the applicant. The Panel also notes that infertility is clinically defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild et al., 2009).

In this context, the Panel assumes that the disease that is the subject of the application is male infertility and that the target population for the claim includes males wishing to increase their fertility but excludes males with clinical infertility.

According to the applicant, 'reduction of sperm DNA damage may contribute to the fertility of men. Sperm DNA integrity may be affected by DNA fragmentation and formation of DNA adducts (primary and secondary structure) and DNA decondensation (tertiary structure). Sperm integrity may be measured by a number of methods, e.g. sperm chromatin structure assay (SCSA), the deoxynucleotidyl transferase-mediated dUTP nick and labelling assay (TUNEL), the single-cell gel electrophoresis assay (the comet assay) and the sperm chromatin dispersion test (SCD). Several studies have shown that increased sperm DNA damage (measured e.g. by DFI and SDI) is associated with decreased embryo quality, decreased pregnancy rates and higher rates of spontaneous miscarriage'.

Upon a request from EFSA to provide evidence that a modification of the risk factor (sperm DNA damage) prospectively modifies the risk of the disease (male infertility), the applicant did not identify any studies supporting this effect. The Panel notes that the applicant did not provide evidence to establish that a reduction of sperm DNA damage decreases the risk of male infertility.

As stated in the EFSA general guidance on health claims applications (EFSA NDA Panel, 2016), if there is no evidence from intervention studies that a reduction of the risk factor generally reduces the incidence of disease, but there is evidence for an independent association between the proposed risk factor and the incidence of the disease from observational studies and the involvement of the risk factor in the development of the disease is biologically plausible, a reduction of the risk factor may be considered a beneficial physiological effect in the context of a reduction of disease risk claim. In this case, evidence that the dietary intervention with the specific food/constituent induces both a reduction of the risk factor and a reduction of the risk of disease (preferably in the same study), needs to be provided.

In the context of this application, therefore, the Panel considers that the reduction of DNA sperm damage is a beneficial physiological effect in the context of reducing the risk of male infertility, as long as evidence is provided that Condensyl® induces a reduction in both DNA sperm damage and male infertility.

3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline, and Google scholar with the following key words: "Condensyl", "sperm DNA fragmentation", "sperm nuclear decondensation", "fertility". No restrictions were applied. A manual search was also performed.

The applicant provided four human intervention studies as being pertinent to the claim.

One study (Cornet et al., 2015) evaluated the effects of Procrelia Man™, a product not complying with the specifications given in Section 3.1 for the food for which the claim is proposed. Another was a single-arm study conducted in males with established clinical infertility with no control group (Dattilo et al., 2014). Both studies were conducted in males with established clinical infertility and two unsuccessful assisted reproductive technology (ART) procedures. The third publication reported on one case of successful pregnancy after 2 years of Condensyl® consumption by the male in a couple with a history of infertility (Junca et al., 2012). The fourth study (Amar et al., 2015) was a parallel, three-arm, non-randomised, open-label study which compared the effect of Condensyl® alone with the effects of a sequential treatment with Fertibiol® and Condensyl® and with no treatment (control). All male participants were under consultation for primary infertility (duration > 3 years) with previous *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI) attempts.

The Panel notes all these studies were conducted in males with established clinical infertility and that they relate to the treatment of the disease, and therefore, the effect of the intervention on the incidence of male infertility cannot be assessed. In addition, the Panel notes that two of these studies had no control group (Junca et al., 2012; Dattilo et al., 2014), and that a third study was conducted with a product not complying with the specifications given in Section 3.1 for the food for which the claim is proposed (Cornet et al., 2015). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

In the absence of evidence for an effect of Condensyl® in reducing sperm DNA damage and the risk of male infertility *in vivo* in humans, the studies provided by the applicant on the proposed mechanisms by which Condensyl® could exert the claimed effect were not considered by the Panel for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Condensyl® and reduction of DNA sperm damage in the context of reducing the risk of male infertility.

4. Conclusions

On the basis of the data presented, the Panel concludes that:

- the food/constituent, Condensyl®, which is the subject of the health claim, is sufficiently characterised.
- the claimed effect proposed by the applicant is 'reduction of sperm DNA damage (sperm nuclear decondensation index and DNA fragmentation index); high sperm DNA damage being a risk factor for male subfertility/infertility'. The target population proposed by the applicant is 'males in reproductive age with unknown reason leading to subfertility'. The Panel assumes that the disease that is the subject of the application is male infertility and that the target population for the claim includes males wishing to increase their fertility but excludes males with clinical infertility. Reduction of sperm DNA damage is a beneficial physiological effect in the context of reducing the risk of male infertility.
- A cause and effect relationship has not been established between the consumption of Condensyl® and reduction of sperm DNA damage in the context of reducing the risk of male infertility.

Steps taken by EFSA

1) Health claim application on Condensyl® and decrease of sperm DNA damage pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 04450_FR). Submitted by Laboratoire Nurilia, 78/80 rue Boileau, 69000 Lyon, France.
2) This application was received by EFSA on 18/10/2016.
3) The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
4) The scientific evaluation procedure started on 21/11/2016.
5) On 12/12/2016, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 15/12/2016 and was restarted on 28/2/2017, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
6) On 28/2/2017, EFSA received the applicant's reply (which was made available to EFSA in electronic format on 28/2/2017).
7) During its meeting on 4/4/2017, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to Condensyl® and decrease of sperm DNA damage in the context of reducing the risk of male infertility.

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Abbreviations

ART	assisted reproductive technology
CBS	cystathionine β-synthase
DFI	DNA Fragmentation Index
GSH	glutathione
ICSI	intra-cytoplasmic sperm injection
INF	*in vitro* fertilisation
SAM	*S*-adenosyl methionine
SCD	sperm chromatin dispersion
SCSA	sperm chromatin structure assay
SDI	nuclear decondensation index
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling